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ATTORNEY DOCKET NO. 2003028-0048 (Ariad 331D USD1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Schreiber & Crabtree	Examiner:	Vogel
Serial No.:	09/834,424	Art Unit:	1636
Filed:	April 13, 2001		
For:	METHODS AND MATERIALS INVOLVING DIMERIZATION-MEDIATED REGULATION OF BIOLOGICAL EVENTS		

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July 22, 2004 — Date
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Kathy Hart Gagnon
Typed or Printed Name of person signing certificate

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Applicant appeals to the Board of Patent Appeals and Interferences (the "Board") from the Examiner's rejection of claims 8-29. A notice to this effect was filed pursuant to 37 C.F.R. § 1.191(a) on December 19, 2003. The stamped return postcard that was filed with the Notice was received by Appellant indicating that the Notice was received by the Patent and Trademark Office on December 22, 2003.

Filed herewith is a Petition under 37 C.F.R. § 1.136 for a five (5) month extension of time, from February 22, 2004, up to and including July 22, 2004, to file this Appeal Brief (the "Brief"). Pursuant to 37 C.F.R. § 1.192(a), this Brief is being filed in triplicate. Also enclosed are checks to cover the $2010.00 fee under 37 C.F.R. § 1.17(a)(5) for the Petition and the $330.00 fee under 37 C.F.R. § 1.17(c) for the Appeal Brief. Please charge any additional fees (or credit any overpayment), to our Deposit Account 03-1721.

Real Parties in Interest

As a result of assignments by the inventors in parent application U.S. Serial No. 09/430,508 (filed October 29, 1999), the real parties in interest in this application are the President and Fellows of Harvard College ("Harvard") and the Board of Trustees of Leland S. Stanford Junior University ("Stanford"). The assignments to Harvard and Stanford were recorded in the Patent and Trademark Office on March 20, 2000 at Reel 010691, Frames 0402 and 0291, respectively.

Related Appeals and Interferences

No other appeals or interferences are known to Appellant, Appellant's legal representative, or Appellant's assignee that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no such appeals or interferences are known that may have a bearing on the Board's decision in this appeal.

Status of Claims

The application was filed with claims 1-7. Claims 1-7 were canceled in an Amendment filed April 1, 2003; claims 8-29 were added. Claims 8-29 were finally rejected in an Office Action mailed July 7, 2003. The rejection of claims 8-29 is hereby appealed. A listing of pending claims 8-29 is provided as **Attachment I**.

Status of Amendments

No after-final Amendments have been submitted by Appellant.

Summary of Invention

Dimerization (or generally oligomerization) of proteins is a biological control mechanism that contributes to the activation of cell surface receptors, transcription factors, vesicle fusion proteins and other classes of intra- and extracellular proteins. The present invention is directed to methods that regulate the dimerization of such endogenous proteins using non-peptidic "dimerizing" agents. Pending claims 8-29 relate to *methods for preparing* these "dimerizers". One such method involves preparing a dimerizer which includes a first non-peptidic moiety that binds to one of the protein mediators covalently linked with a second non-peptidic moiety that binds to the other protein mediator. The resulting dimerizer binds to both protein mediators. Claim 8 is drawn to embodiments in which the protein mediators are cell-surface receptors. Claim 19 is drawn to embodiments in which the protein mediators are different and the first and second moieties of the dimerizer are different. Claims 9-18 and 20-29 depend from claim 8 and/or claim 19.

Issues

The sole issue on appeal is whether claims 8-29 are invalid for lack of written description.

Grouping of Claims

Claims 8-29 stand or fall together.

Argument

Claims 8-29 are not Invalid for Lack of Written Description

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if the patent specification sets forth enough detail to "allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 at 928 (Fed. Cir. 2004).

Here, Appellant is claiming *methods for preparing* a dimerizing agent ("dimerizer"). The patent specification (see, for example page 13, line 4 - page 15, line 3; see also page 19, line 10 - page 21, line 19) makes perfectly clear that the invention encompasses methods for preparing *any* dimerizer that includes two covalently linked non-peptidic moieties each of which binds to the same or a different protein mediator (e.g., a cell surface receptor), as required to describe the broadest of the pending claims (e.g., claims 8, 9, 12 and 19-21). The specification also specifically recites relevant subsets of cell surface receptors that can act as protein mediators as recited in claims 10, 11 and 18 (see, for example, page 3, line 27 - page 4, line 9; page 4, lines 19-23; page 5, lines 17-20; page 7, line 22 - page 10, line 23). Likewise, the specification specifically points to dimerizers having the characteristics recited in claims 13-17 (see, for example, page 11, line 13 - page 12, line 14); describes the specific biological events that are recited in claims 22-27 (see, for example, page 4, lines 7-9; page 5, lines 26-29; page 7, lines 23-25; page 12, line 25 - page 13, line 2; page 29, line 16 - page 33, line 19); and describes the pharmaceutical compositions that are recited in claims 28 and 29 (see, for example, page 28, lines 21-29). The present specification and claims as originally filed clearly put the public on notice that the inventors considered the presently claim methods to be within the scope of their invention. A skilled artisan would therefore understand the scope of the claimed method.

Furthermore, as Appellant has previously discussed, those skilled in the art would have fully appreciated and understood the present specification as properly describing the claimed invention. In particular, they would have recognized that at the time of filing it was trivial and routine to provide or identify moieties that bind to a protein. Thus, they would have appreciated that the inventors, and indeed other practitioners of this art, were in possession of non-peptidic

moieties having a wide variety of chemical structures that could be used as components of dimerizers for use in accordance with the present invention. As highlighted in the specification, numerous protein-binding compounds were well known in the art as were technologies for selecting such compounds. All this would have been readily appreciated by the practitioner of ordinary skill in the art. Preparing a dimerizer in which such protein-binding compounds were covalently linked together was also a given. It is and was within the level of the skilled artisan.

Appellant has previously pointed out that, since the filing of the present application, other researchers have identified and used non-peptidic agents that dimerize receptors (as described in appellant's specification), and have immediately recognized that their success with a given receptor and small-molecule dimerizer is broadly generalizable to other receptors and dimerizers as well. In a prior submission, Appellant has specifically pointed to the Qureshi reference (*Proc. Natl. Acad. Sci. USA* 96:12156, 1999), in which researchers at Merck presented their first example of an agent that could dimerize the erythropoietin receptor (EPOR) and concluded:

> "...it does validate the concept that the EPOR, and by extension most cytokine receptors, can be ligated together in an active conformation by a nonpeptidyl molecule. The only requirement is that the small molecule must be able to interact with both chains of the receptor. This paper also lays out a basic strategy for identifying cytokine mimetics by converting an antagonist into an agonist." (Qureshi et al., last sentence, page 12161).

Appellant has also made reference to the Tian reference (Tian et al., *Science* 281:257, 1998), in which researchers at Ligand Pharmaceuticals and SmithKline Beecham showed that a non-peptidic small molecule can dimerize the granulocyte-colony-stimulating factor receptor and concluded:

> "Our findings indicate that a small molecule can trigger the activation of a large (~120 kD) receptor protein that requires dimerization for activation, through a domain not involved in binding the natural ligand." (Tian et al., last sentence, page 259).

The Examiner has dismissed these references as irrelevant:

> "[These references do not] provide evidence that the inventors, at the time the application was filed, were in possession of the invention as claimed. It is noted that the non-peptidic binding small molecules taught by the references, in fact, aren't described in the instant specification, therefore their description by others is not relevant to the instant application." (page 4 of Office Action mailed July 7, 2003).

The Examiner has misunderstood Appellant's point. Appellant provided these references as objective evidence of the skilled artisan's expectations in this field. The fact that two independent groups of researchers recognized that a successful result in a single proof-of-principle experiment in this area is broadly generalizable is highly relevant to the issue in this case. Indeed, as noted above, the written description requirement is satisfied if the patent specification sets forth enough detail to "allow a person of ordinary skill in the art to [...] recognize that the inventor invented what is claimed." The fact that Qureshi et al. and Tian et al. relied upon the same sort of language as Appellant makes it plain that, at least in this art, Appellant's language is and was reasonably, appropriately and sufficiently descriptive to put the public on notice of Appellant's possession of the invention. Requiring Appellant to use language other than that which is reasonable in their art cannot be consistent with the intent or effect of the description requirement.

In particular, against the backdrop of real-life conclusions and expectations made by Qureshi et al. and Tian et al., and in view of the nature and broad applicability of the claimed invention, an overly rigid request for structure disclosure misses the mark. The Examiner's written description standard would require Appellant to include a picture or name of every chemical entity that binds an endogenous protein mediator and could be included in a dimerizer for use in accordance with the present invention. Those of ordinary skill do not need such information. They understand from the specification that any of a variety of moieties can be used in preparing dimerizers. From the teachings of the specification, they understand and recognize the full scope of what Appellant has invented. Clearly objective evidence of the expectations and understanding of actual practitioners like Qureshi et al. and Tian et al. are of *great* relevance here and should be given much greater weight than unsupported, subjective conclusions by the PTO. In short, the present specification provides sufficient description concerning the identification of those moieties whose use fall within the scope of the present claims; further description is neither necessary nor appropriate.

For all of the foregoing reasons, Appellant respectfully requests that the rejection for lack of written description be withdrawn.

Conclusion

Appellant again concludes with the belief that claims 8-29 are well supported by the specification. Allowance of the pending claims is earnestly requested.

Respectfully submitted,

Dated: July 22, 2004

Charles E. Lyon, D.Phil.
Limited Recognition Under 37 C.F.R. § 10.9(b)

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Pending Claims

1-7. **(Canceled)**

8. **(Previously presented)** A method for preparing an agent that effects a biological event mediated by the association of two or more endogenous cell surface receptors, the method comprising preparing an agent which includes a first non-peptidic moiety that binds to one of the cell surface receptors covalently linked to a second non-peptidic moiety that binds to the other cell surface receptor, wherein the agent binds to both cell surface receptors.

9. **(Previously presented)** The method of claim 8 wherein the biological event is mediated by the association of two or more molecules of the same cell surface receptor and the first and second non-peptidic moieties are the same.

10. **(Previously presented)** The method of claim 9 wherein the cell surface receptor is a receptor for a cytokine, growth factor or other hormone.

11. **(Previously presented)** The method of claim 10 wherein the cell surface receptor is a receptor for erythropoietin ("EPO"), granulocyte colony stimulating factor ("G-CSF"), thrombopoietin ("TPO"), growth hormone ("GH"), interleukin-2 ("IL-2"), interferon-alpha, interferon-beta, or a neurotropic factor.

12. **(Previously presented)** The method of claim 8 wherein the biological event is mediated by the association of molecules of two different cell surface receptors and the first and second moieties are different.

13. **(Previously presented)** The method of claim 8 wherein the first and second non-peptidic moieties bind to cytoplasmic portions of the cell surface receptors.

14. **(Previously presented)** The method of claim 8 wherein the first and second non-peptidic moieties bind to extracellular portions of the cell surface receptors.

15. **(Previously presented)** The method of claim 8 wherein the agent binds to the cell surface receptors with a $K_d \leq 10^{-6}$ M.

16. **(Previously presented)** The method of claim 8 wherein the first and second non-peptidic moieties have a molecular weight less than 5 kD.

17. **(Previously presented)** The method of claim 8 wherein the agent is membrane permeant.

18. **(Previously presented)** The method of claim 8 wherein the cell surface receptors are selected from the group consisting of epidermal growth factor-receptor (EGF-R), ataxia telangiectasia and rad-related 2/neuroblastoma oncogene (ATR2/neu), hermaphrodite homolog-2/neuroblastoma oncogene (HER2/neu), hermaphrodite-3/cellular-erythroblastic leukemia oncogene homolog-3 (HER3/c-erbB-3), Xiphophorus melanoma receptor tyrosine kinase homolog (Xmrk); insulin-like growth factor-I-receptor (IGF-1-R), insulin receptor-related receptor (IRR); platelet-derived growth factor receptor-a (PDGF-R-a), platelet-derived growth factor receptor-ß (PDGF-R-ß), colony stimulating factor-1-receptor (CSF-1-R, macrophage-colony stimulating factor-receptor (M-CSF-R)/cellular-McDonough feline sarcoma homolog (c-Fms)), c-kit (Steel Factor Receptor, mast/stem cell growth factor receptor, HZ4-feline sarcoma virus viral oncogene homolog), serine/threonine kinase/fms-like tyrosine kinase 2 (STK-1/Flk-2); fibroblast growth factor-receptor FGF-R (FGF-R), [acidic-] fibroblast growth factor-receptor-1 (flg), [basic-] fibroblast growth factor-receptor-2 (bek); neurotrophic tryosine kinases; cell-surface determinant-3-z (CD3-z) and cell surface/class II determinant-3-e (CD3-e); ß and g chains of Fc/IgE receptor-1 (FCERI); g chain of Fc receptor/cell-surface determinant-16 (Fcg-RIII/CD16); cell-surface determinant-3-g, -d and -e subunits (CD3-g, -d and -e); Ig-a subunit of B-cell antigen receptor complex/membrane-bound, Ig-associated protein-1 (Ig-a/MB-1) and Ig-ß subunit of B-cell antigen receptor complex/c membrane-bound, Ig-associated glycoprotein B29 (Ig-ß /B29); the common ß subunit shared by the granulocyte/macrophage-colony stimulating factor (GM-CSF), interleukin-3 (IL-3) and interleukin-5 (IL-5) receptors; the ß chain of glycoprotein MW 130 KD (gp130) associated with the interleukin-6 (IL-6), leukemia inhibitory

factor (LIF), ciliary neurotrophic factor (CNTF), oncostatin M, and interleukin-11 (IL-11) receptors; the interleukin-2 (IL-2) receptor gamma subunit associated also with receptors for interleukin-4 (IL-4), interleukin-7 (IL-7) and interleukin-13 (IL-13); the ß chain of the interleukin-2 (IL-2) receptor; receptors for interferons (IFN) a/ß and g; receptors for growth hormone (GH), erythropoietin (EPO) and prolactin; and the Transforming growth factor-ß (TGF-ß) family of cell surface receptors.

19. **(Previously presented)** A method for preparing an agent that effects a biological event mediated by the association of two or more endogenous protein mediators, the method comprising preparing an agent which includes a first non-peptidic moiety that binds to one of the protein mediators covalently linked with a second non-peptidic moiety that binds to the other protein mediator, wherein the agent binds to both protein mediators, the biological event is mediated by the association of molecules of two different protein mediators and the first and second moieties are different.

20. **(Previously presented)** The method of claim 19 wherein at least one of the protein mediators is a cell surface receptor.

21. **(Previously presented)** The method of claim 19 wherein the two different protein mediators are cell surface receptors.

22. **(Previously presented)** The method of claim 19 wherein the biological event is transcriptional regulation, the first non-peptidic moiety binds to a protein containing a DNA-binding domain and the second non-peptidic moiety binds to a protein containing a transcriptional regulatory domain.

23. **(Previously presented)** The method of claim 22 wherein the transcriptional regulatory domain is a transcriptional activation domain.

24. **(Previously presented)** The method of claim 22 wherein the transcriptional regulatory domain is a transcriptional repression domain.

25. **(Previously presented)** The method of claim 19 wherein the biological event is translocation of a selected protein to a predetermined cellular component, the first non-peptidic moiety binds to the selected protein and the second non-peptidic moiety binds to a constituent of the predetermined cellular compartment.

26. **(Previously presented)** The method of claim 25 wherein the first non-peptidic moiety binds to a protein that functions only in the cytoplasm and the second non-peptidic moiety binds to a constituent of the nucleus or mitochondrion.

27. **(Previously presented)** The method of claim 19 wherein the biological event is destruction of a selected protein, the first non-peptidic moiety binds to the selected protein and the second non-peptidic moiety binds to a constituent of the proteasome.

28. **(Previously presented)** The method of claim 8 or 19 further comprising mixing the agent with a pharmaceutically acceptable carrier and optionally with one or more pharmaceutically acceptable excipients.

29. **(Previously presented)** A method which comprises providing an agent prepared according to the method of claim 8 or 19 and mixing the agent with a pharmaceutically acceptable carrier and optionally with one or more pharmaceutically acceptable excipients.